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Quantitative techniques found to be useful in characterizing the complex attractors of dynaimcal systems and the non-convergent distribution functions of statistical hierarchies were applied to the problem of drug-induced phase-transitions in patterns of exploratory behavior in the rat. Methods derived from ergodic theory and the application of scaling exponents proved to be particularly useful. These techniques provided discriminations among drug effects and insights into behavioral mechanisms that were not accessible using traditional psychopharmacological measures.

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FINAL REPORT

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THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

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The original proposal for this project listed three principal goals:

1. Further elaboration and application of the quantitative techniques of modern dynamical systems theory and experimental mathematics to sequential data or "time series".

2. Numerical exploration of both smooth and discrete abstract dissipative dynamical systems as realistic low-dimensional compressions of the dynamical response pattern to increasing doses of stimulants.

3. Development of phase-space graphic computer programs for the qualitative description of changes in complexity induced by stimulant and other drugs in r ıronal, neurochemical, and behavioral dynamical systems.

Data were to be generated in three laboratories studying the effects in rats of stimulants and other parametirci perturbations on: (a) locus coeruleus, substantia nigra, and cortical neuron interspike intervals; (b) continuously HPLC(ec)-monitored levels of NE, MHPG, DA, DOPAC, HVA, 5HT, and 5HIAA in brainstem perfusion studies of freely moving rats; (c) digitally resolved temporal and spatial exploratory behavior in conjunction with (b). The laboratories to be involved were those of Drs. Stephen Foote (a), Ronald Kuczenski (b), and David Segal (c) of UCSD. The shared interests of these investigators in brainstem biogenic amine-mediated neurobiological mechanisms of behavior and the use of cocaine, amphetamine, and other pharmacological probes of mechanisms was expected to permit cross-level exploration for the dynamical universality predicted by the theory.

As the project progressed, some alterations in the emphasis of the project were required. The fundamental premise of the project was to assess the utility of applying non-linear dynamical methods to high-quality biological data. That general objective of the project was accomplished. However, the specific databases upon which these methods were proposed to be developed were not all used effectively. Specifically, the planned use of time series data derived from Dr. Kuczenski's HPLC analyses of neurochemical changes in freely moving rats never materialized. Similarly, no substantive progress was made using data from Dr. Segal's locomotor activity chambers. Some promising work has been accomplished in collaboration with Dr. Foote, using his measures of single unit responses of cells in the locus coeruleus, substantia nigra, and cortex of rats. This work is currently in manuscript form and should be submitted for publication within the year.

In some of our more strictly theoretical work, we demonstrated some dynamical consequences of making the formal characteristic of neuronal elements and their connectivities more realistic than those of modern neural computer algorithms [3]. Specifically, we studied two multiplicatively coupled logistic maps, each with the quadratic response characteristics of neurons with autoreceptor mechanisms, which iteratively exchange their outputs. The dynamic phenomenology of this two-neuron system, though noninvertible, demonstrated characteristics of both automorphisms of the real

line and diffeomorphisms of the plane, with smooth parametric transitions between them. We portrayed a unified parameter space containing the negative, positive, and mixed-coupled regimes, categorized the phase space structures using characteristic exponent inequalities, explored representative parametric paths, demonstrated generic bifurcation sequences, and reported number theoretic ordering in parameter space. We conjectured that most, if not all, "middle-layer-like" brain systems, in contrast to primary sensory and motor information transport systems, are dominated by intrinsic dynamics of the sort we demonstrated. According to this view, external input serves as a perturbation of these already ongoing complex systems. The intrinsic instabilities of these middle-layer dynamics return the unpredictability required by theroetical studies of real brain functions to models of neural networks. We demonstrated a variety of parameter-dependent intrinsically ordered attractor sequences and number theoretic series which emerge from the global dynamics and exemplify the rich dynamical "machine" language potential for specific coding by brain-like information transport and learning algorithms.

Another theoretical development was pursued to examine the statistical properties of real macromolecular sequences using an approximation based on the composition of two ergodic sets [2]. Both varied and reliable mechanisms of information transport in molecular biological systems can be obtained from the universality properties of continuous and discrete dynamical systems whose output has the general properties of a set which combines sensitivity to initial conditions and indecomposability with a positive density of periodic points. This approach required a revision of information theory for macromolecular systems dictated by their failure to fulfill the conditions of Shannon's existence proof: there exists a one-to-one mapping that makes the channel capacity finite. Relaxation studies of polypeptides, proteins, and nucleotides demonstrate a lack of characteristic times. Using calcitonin as the exemplar, a more appropriate statistical approach to macromolecular coding was explored using a hyperbolic distribution with an infinite multiplicity of moments, multiplicative noise, and belonging to the family of convolutionally stable distributions without finite mean or variance [2]. This work used a phase space reconstruction technique to relate the potencies of important calcitonin analogues to the global "tightness" of the vorticity.

The most significant work related to concrete biological systems was based on the data from Dr. Geyer's Behavioral Pattern Monitor (BPM) system, which provided the pilot data on behavioral measures presented in the original proposal. The extensive database derived from the BPM system proved to be ideal for addressing the conceptual questions originally proposed. Thus, we had considerable success by carefully examining data from studies of the behavioral profiles of psychoactive drugs as characterized in the BPM system. In particular, we developed new methods based on procedures developed in the context of theoretical physics and non-linear dynamics. Using a k-D splitting algorithm, we described the initial demonstrations of the utility of complexity and entropy measures in biological applications, using data from the BPM system [7]. Measures of complexity derived from ergodic theory of dynamical systems were developed and applied to an exemplary data set describing locomotor movements of rats in a bounded space. A symbolic dynamical system was obtained by partitioning the event space into equally probable partition elements, using a k-dimensional tree. The measures calculated from the symbolic sequences included the topological entropy (ht)--i.e., the rate of increase of all possible sequences with increasing sequence length--and the metric entropy (hm)--i.e., the rate of increase of all likely sequences with increasing sequence length. These measures were used to assess changes in rat locomotor behavior as recorded in the behavioral pattern monitor (BPM) that were induced by amphetamine (0.25, 0.50, 1.0, or 2.0 mg/kg) and 3,4-methylenedioxymethamphetamine (MDMA; 1.25, 2.5, 5.0, or 10.0 mg/kg). Amphetamine increased the mean activity, ht, and hm. MDMA resulted in a monotonic dose-response curve for

activity but exhibited a biphasic dose response in ht and hm. In particular, some animals in the higher dose groups showed a ht in the range of the saline controls, whereas other animals exhibited a significantly reduced ht and a greater decrease in hm, suggesting that two different behavioral reactions coexist within the same higher dose range of MDMA. An important implication of our method is that, in applied ergodic measure-theoretic approaches, the partition that determines the elements of the symbolic dynamical system should not be specified a priori on abstract mathematical grounds but should be chosen relative to its significance with respect to the data set in question. Here, the animal constructs its own spatiotemporal partition in behavioral phase space.

In addition to the complexity and entropy measures, we also made great progress in the use of scaling measures to provide more sensitive characterizations of drug effects. We used scaling measures to provide more sensitive characterizations of drug effects [4,6]. Conceptually, these measures are derived from the concept of dimensionality in the field of fractal geometry. We have defined two global scaling measures from our BPM data, one characterizing the temporal structure of the animal's behavior, the other being sensitive to changes in the geometrical structure of the animal's locomotor path. These two measures enable us to assess quantitatively similarities and differences between different drug treatments. The first full description of this approach appeared in Psychopharmacology [6]. This paper details the derivations and applications of the temporal scaling exponent, *alpha*, and the spatial scaling exponent, *d*, and introduces the *d-alpha* plane. Basically, *alpha* assesses the level of activity of an animal and has proven to be more consistent and sensitive than the traditional measure of photobeam breaks, presumably because it utilizes all the available information. The spatial scaling exponent *d* describes the roughness of the path traversed by the animal - it assesses the average geometrical information contained in locomotor activity in a manner that is independent of changes in the amount of activity. The *d-alpha* plane provides a condensed way to present and visualize a large amount of information about the nature of a drug's effects across a range of doses and facilitates comparisons between the effects of different drugs. To illustrate this feature of our approach, we compared the effects of a variety of psychostimulant drugs and used these comparisons to address hypotheses regarding the behavioral processes affected by these drugs [4,5,6].

A variety of psychoactive substances (amphetamine, nicotine, scopolamine, apomorphine, lisuride, and MDMA) were tested to examine whether a scaling hypothesis is appropriate for the description of the amount and the structure of rat locomotor paths recorded in the BPM [6]. The analytical approach was based on the assumption that the scaling behavior of a few collective variables may characterize sufficiently changes in the animal's behavior induced by different drugs. The temporal scaling exponent alpha, describing the ratio of fast to slow responses in the BPM, sensitively reflected the different stimulant properties of the substances. The spatial scaling exponent d, which relates the average path length to the resolution used to measure consecutive responses, was found to discriminate substances that had been separated previously via qualitative descriptions. Several behavioral response categories emerged from comparisons of the locations of different drugs on a two-dimensional d-alpha plane. Scopolamine, MDMA, lisuride, and high doses of apomorphine increased alpha while decreasing d, whereas amphetamine, nicotine, and caffeine produced an increased alpha with no change or an increase in d. Stereotypies could be identified on the opposite ends of the spatial scaling exponent scale and were interpreted as reflecting two kinds of perseveration. These results suggest that scaling approaches can be used to assess quantitatively the state of the animal based on its locomotor behavior and that the exponents can serve as collective variables providing a macroscopic description based on the microscopic elements of behavior.

Using both our traditional measures and the newer theoretically driven measures, we explored the mechanisms contributing to the locomotor hyperactivity induced by MDMA [1,5]. We

discovered that the profound locomotor activation produced by MDMA and related drugs is not due primarily to dopamine release, but is due to serotonin release [1]. We blocked MDMA-induced hyperactivity with the selective serotonin uptake blockers fluoxetine, sertraline, or zimelidine or with the serotonin synthesis inhibitor PCPA. By contrast, these pretreatments either potentiated or had no effect on the hyperactivity induced by the dopamine releasing agent amphetamine. Conversely, the catecholamine synthesis inhibitor AMPT, which blocks the effects of amphetamine, did not affect the response to MDMA. We applied our scaling and complexity measures to this problem [5]. The use of scaling measures enabled us to further differentiate the effects of MDMA from those of either amphetamine or hallucinogens. In addition, comparisons of the behavioral effects of MDMA across both repeated tests and repeated administrations of the drug confirmed that our spatial scaling exponent, d, was affected differently from more traditional measures. Furthermore, d proved to be the most sensitive of our various measures of the effects of serotonin releasers on the spatial structure of the locomotor paths exhibited by the animals. The combination of our new and old measures of drug effects on behavior clearly provides more information than can be obtained by reliance on any one set of measures.

The *d-alpha* plane was also used to systematically compare various methylenedioxy-substituted phenethylamines having varying potencies as releasers of dopamine or serotonin [5]. This analytical approach enabled us to make discriminations between drugs and specific enantiomers of drugs that have previously required much more elaborate and time-consuming procedures such as drug-discrimination tests. With this approach, we can characterize and quantify different drug effects in a single test session using a procedure that does not require repeated administrations of the drug to the animals. Thus, the effects of chronic versus acute exposures to the drugs can now be assessed reliably.

In further work, we developed modified versions of both the scaling measures and the previously published entropy measures. These extensions include the generalization of the entropy as well as the spatial scaling exponent, *S(h)* and *f(d)* respectively. These extensions allow us to not only describe the average scaling measure but enables us to assess quantitatively the contribution of different subsets to the overall behavior. This approach is based on the idea that the animals engage in different "types" of behavior which can be quantitatively described by different local scaling exponents. For example, a rat moving along the wall in a straight path may also engage in highly repetitive head movements or gnawing stereotypies. We have observed precisely this type of behavior in rats treated with 20.0 mg/kg cocaine. However, the averaging procedure yielding the average spatial scaling exponent *d* would not capture the distinctly different characteristics of these behavioral "subsets". Thus, using the spectrum of spatial scaling exponents, *f(d)*, we can now assess these behavioral subsets in addition to the average geometrical path structure [4]. The singularity spectrum of local entropies ($ S ~ (~ alpha ~) $) computed from the microcanonical dynamical partition function was used to describe the sequential dynamical structure of rat locomotor paths under the influence of cocaine. The approach used was analogous to the microcanonical ensemble of statistical mechanics and permitted the sensitive detection of "phase transition" like behavior. The results suggest that the behavioral sequences exhibited by the rats are determined by two processes, each with its own entropy $ (~ alpha sub {l} ~ , ~alpha sub {h} ~) $. These processes are changed simultaneously by cocaine, suggesting that they coexist as local repellers with overlapping insets and undergo a change from second to first order phase transition [8]. With this approach we may be able to differentiate between different drugs, e.g. MDMA, high doses of cocaine, or scopolamine, generating an overall increase in straight path patterns but acting presumably via very different mechanisms. These elaborations have already led to even more precise insights into mechanisms underlying the

behavioral effects of psychoactive drugs.

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Mandell, A.J.: An unstable singularity theory of molecular biological coding: Calcitonin's structures and potencies. In: *Dynamic Patterns in Complex Systems*. Eds. J.A.S. Kelso, A.J. Mandell, and M.F. Shlesinger. World Scientific, Singapore, pp 219-235, 1988.

Paulus, M.P., Gass, S.F. and Mandell, A.J.: A realistic, minimal "middle-layer" for neural networks. *Physica D*, 40:135-155, 1989.

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PERSONNEL

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